REMARKS

Claims 2, 5-7, 14, 15, and 17 are pending in the application. Claims 1, 3-4, 8-13, 16, and 18-49 having been canceled.

Claims 2, 5-7, and 14-15 are rejected under 35 U.S.C. §112, first paragraph as not being enabled.

Claims 2, 5-7, and 14 are rejected under 35 U.S.C. §102(e) as being anticipated by Dorwald et al. (U.S. Patent No. 7,208,497)

Claim 15 is rejected under 35 U.S.C. §103(a) as being unpatentable over Dorwald et al.

Claim 17 is allowed.

Introduction

Applicants acknowledge receipt of the Office Action mailed August 21, 2009. No new matter has been added with the present Response. Applicants respectfully request reconsideration based on the remarks presented herein.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner asserted that although the specification is enabled for the claimed chemical compounds per se or salts of the claimed compounds per se, it does not reasonably provide enablement for solvates of the claimed compounds.

Applicants respectfully traverse.

Although the Examiner cites the *Wands* factors, Applicants respectfully assert that the basis upon which the Examiner has made the enablement rejection in the present case is in fact inconsistent with the standard set out in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants remind the Examiner that the standard for determining whether a claim is enabled is whether one can make and use the claimed invention without undue experimentation. No one *Wands* factor can be used by itself to assert that a claim is not

enabled. Rather, it is the totality of the *Wands* factors that determine whether a claim is enabled or not. Moreover, as noted above, the initial burden is on the Examiner to present evidence asserting why the claims are not enabled.[1] For the reasons detailed below, Applicants submit that the Examiner has not met this burden.

As exemplified in the references cited below, there was substantial methodology available for the generation of solvate at the time Applicants' application was filed.

The Examiner stated that the specification does not provide an example of a solvate or a procedure for forming one. Applicants remind the Examiner that the Federal Circuit has held that one need not disclose, and should preferably omit that which is well known in the art. See e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367 (Fed. Cir. 1986); *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co*., 730 F.2d 1452 (Fed. Cir. 1984). Applicants herein provide several references that were available at the time Applicants' application was filed that provide standard and reproducible protocols for the preparation of solvates. These references are discussed in more detail below.

Furthermore, Applicants remind the Examiner that there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 422 F.2d 904 (C.C.P.A. 1970); *Ex parte Nardi*, 229 USPQ 79 (Pat. Off. Bd. App. 1986). As discussed in more detail below, given that one skilled in the art could make and identify various solvates of a particular organic molecule using routine methods known in the art at the time of the invention, working examples are not required to enable the invention.

The Examiner further asserted that the formation of solvates are unpredictable. First, Applicants note that "predictability" is only one of the *Wands* factors. Predictability, by itself, is not dispositive of enablement.

The Examiner cited Vippagunta et al., Advanced Drug Delivery Reviews, 2001, 48:3-26 (hereinafter "Vippagunta") for the proposition that "[p]redicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult." Applicants are not attempting to predict

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[1] In *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), the court stated, "it is incumbent upon the Patent Office, whenever a rejection on this [enablement] basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

exactly how solvate molecules become incorporated into a crystal lattice of a claimed compound. Applicants are simply claiming that such compounds are within the scope of Applicants' invention for using compounds.

Also, Applicants note that Vippagunta, in another passage, acknowledges that polymorphs can be predicted based on the molecular structure of the compound where it is taught that "recent developments in computational chemistry allow the prediction of possible polymorphic forms based only on the molecular structure of the drug." Vippagunta at page 11, second column. Thus, when Vippagunta is viewed as a whole, one can only come to the conclusion that Vippagunta acknowledges that there is some predictability to the formation of solvates.

As discussed below, methods for preparing solvates are well known and routine in the art. Applicants below summarize four references for the Examiner's consideration that further establish the extensive knowledge regarding preparation of solvates available to one of skill in the art prior to the filing date of the present application.

Caira

Caira, M., 1998, "Crystalline Polymorphisms of Organic Compounds," Topics in Current Chemistry 198:164-208 (hereinafter "Caira"), describes "[n]umerous examples of polymorphic systems . . . to illustrate the applications of both older and newer techniques for their [formation and] investigation . . . includ[ing] studies of pseudopolymorphism manifested by hydrates and solvates of the parent organic molecule." Caira at 164. Caira Section 3.1 (pages 177-180) provides also a review of methods of preparing polymorphs and pseudopolymorphs (i.e., solvates), and describes how characterization of polymorphs "normally commences with experimental screening [e.g., by hot stage microscopy] . . . to provide preliminary indications of the presence of crystalline polymorphic and pseudopolymorphic (solvated) . . . forms." *Id.* at 177. Caira also teaches that "[m]ost pseudopolymorphs are prepared by crystallization of the parent organic compound from the respective solvent, whereupon the latter becomes incorporated in the new crystal," and that "[e]xposure of the parent organic compound to vapours may also result in the formation of pseudopolymorphs (as occurs e.g. when anhydrous drugs react with atmospheric water to form hydrates)," and refers to the drug indomethacin as an example. *Id.*

Thus, Caira not only informs one skilled in the art of routine methods that may be used to make a hydrate, but also provides an example of the method. Applicants note that these methods are taught by Caira as routine.

Guillory

Guillory, "Generation of polymorphs, hydrates, solvates, and amorphous solids", in H.G. Brittain, (Ed.), Polymorphism in Pharmaceutical Solids, vol. 95, Marcel Dekker, New York, 1999, pp. 183-226 (hereinafter "Guillory"), describes methods employed to obtain solvated forms of compounds. Guillory is specifically written to teach how to make solvates and other solid state forms of pharmaceutical compounds. The methods employed to obtain hydrate forms and those employed to obtain solvate forms are described in sections II and III of Guillory, beginning at page 202. Guillory teaches that with "due diligence" (see page 186), using methods known in the art will confidently put one of skill in the art in possession of the crystalline forms likely to arise in the normal course of drug development, and provides specific methods one of skill in the art can use to prepare hydrates and solvates. The methods provided in Guillory are not undue experimentation but deliberate protocols that are within the level of one of ordinary skill in the art.

Byrn

Byrn, et al., Solid-State Chemistry of Drugs, 2nd Ed., 1999 SSCI, West Lafayette, IN, (hereinafter "Byrn"), contains a chapter on "Hydrates and Solvates", chapter 11. Tables 11.1 and 11.2 both list numerous pharmaceutical solvates and hydrates. This chapter provides an extensive discussion of the formation of these compositions, providing one skilled in the art knowledge of the methods used to make these solvates.

Each of the above references, Caira, Guillory, and Byrn, as well as Vippagunta (cited by the Examiner) are review articles. As review articles, the references analyze work from a plurality of investigators so as to provide one of skill in the art numerous teachings of how to make and characterize solvates.

Thus, in view of the state and teachings of the prior art, it is apparent that methods of making and characterizing solvates are predictable to one skilled in the art. With the teachings provided in Applicants' specification, and using methods such as those described in Caira, Vippagunta, Guillory, or Byrn, it would require nothing more than routine experimentation to make the solvates claimed.

For at least these reasons, Applicants respectfully submit that the solvates of Applicants' claims are enabled by the specification and request that the Examiner withdraw the enablement rejection of the pending claims.

Comparison to *In re Wands*

Applicants direct the Examiner's attention to the similarities of the facts associated with the presently claimed invention to the facts in *Wands*. The issue in *Wands* was whether the patentee had adequately enabled one skilled in the art to make high-affinity IgM antibodies against HbsAg that were needed to practice the claimed assay methods. *See Wands*, 858 F.2d at 735. The Federal Circuit found that even though screening for hybridomas was labor-intensive with numerous steps (*e.g.*, immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies), all of the methods needed to practice the invention were well-known, and the amount of effort was not excessive enough to be undue, despite any unpredictability associated with making antibodies. *See id.* at 740.

Applicants submit that the formation and characterization of solvates of a given organic molecule requires substantially less experimentation than preparing monoclonal antibodies. For example, preparation of monoclonal antibodies requires months to perform the steps of immunization, isolation of lymphocytes from the spleen of the immunized animal, fusion of lymphocytes with myeloma cells, hybridoma isolation and characterization (often requiring screening of hundreds of separate hybridoma cells), and assay of the antibody secreted from each hybridoma culture. In contrast, formation of a solvate takes only hours to days, and simply requires exposing the compound to a solvent, removing excess solvent, reducing the temperature and seeding for solid formation, and assaying the solid to determine if a solvate has formed.[2] Thus, Applicants submit that the assertion by the Examiner that preparation of solvates would require undue experimentation, while the monoclonal antibodies in *Wands* are enabled, is clearly inconsistent.

While the complexity of the procedures for making monoclonal antibodies and solvates is highly disparate, the processes share the characteristic that the step(s) involved are well-known and routine. As noted in the plurality of review articles cited by Applicants herein, to make solvates, samples of the organic compound are exposed to various different solvents. Once the solvates are formed, they can be readily analyzed by routine methods, including thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer

[2] In addition to the steps described above, there may be several other steps in the production of monoclonal antibodies not described in *Wands* (*e.g.*, preparation of antigen, repeated immunization of animals, testing of animal serum for the presence and titer of the antibodies of choice, introduction of hybridoma cells into animals to induce liquid ascites tumors, draining the ascites tumors from the living animals, purification of monoclonal antibodies from the ascites fluid).

titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of hydrate or solvate molecules in the sample. *See, e.g.,* Vippagunta, at page 18, second column.

Exposure of the organic compounds to various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from solvent. *See also* Caira and Guillory as discussed above. While there may be various solvents and conditions to test, the screening of solvents for the ability to form solvates with a given organic compound merely uses methods that are well-known in the art and straightforward to implement. And, as explained by the court in *Wands*, "the test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Wands* at 737.

Applicants also note that there are numerous companies that offer to provide such screening services (usually combined with polymorph screens). Such companies generally advertise how quickly and efficiently they can screen for solvates. Example companies offering these services include Wilmington PharmaTech (Newark, DE), Avantium Technologies (Amsterdam), and SSCI/Aptuit (West Lafayette, IN).

The Examiner bases the enablement rejection on (1) unpredictability of solvate formation and use and (2) lack of working examples. Although unpredictability was the main reason for the PTO's rejection of the claims in *Wands*, the rejection was reversed by the Federal Circuit because all the methods needed to practice the invention were well-known and the amount of effort was not undue. As in *Wands*, where the court concluded that methods for making monoclonal antibodies were enabled because the methods used were characterized, Applicants have also shown that solvates can be easily made and characterized using routine well known methods.

Accordingly, any unpredictability associated with solvate formation that might exist is clearly outweighed by the fact that preparing and screening for solvates is routine and employs well-known methods.

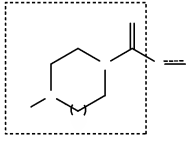
In sum, Applicants respectfully submit that the Examiner has not provided evidence or reasoning that the making and use of solvates is anything but routine in the pharmaceutical industry. Enablement requires only that one can practice the invention without undue experimentation. Enablement does not require the ability to predict with 100% certainty the outcome of any experiment. For at least the reasons detailed herein, Applicants respectfully

request that the rejection of the claims as not enabled under 35 U.S.C. § 112, first paragraph, for solvates be withdrawn.

Rejection Under 35 U.S.C. §102(e)

Claims 2, 5-7 and 14 stand rejected under 35 U.S.C. §102(e) as being anticipated by Dorwald et al. (U.S. Patent No. 7,208,497). The Examiner contends that Dorwald et al. disclose piperazine-containing compounds that read on the instantly claimed compounds of Formula III recited in claim 2. The Examiner specifically references Example 23, namely 3-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-(4-propyl-piperazin-1-yl)propenone. Applicants respectfully traverse this rejection on the grounds that Dorwald et al. cannot anticipate claims 2, 5-7, and 14, because the cited species does not fall within the genus compounds of Formula III.

The examples contained in the cited reference, including (3-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-(4-propyl-piperazin-1-yl)propenone), do not fall within the scope of compounds encompassed by the genus recited in claim 2. Dorwald et al., disclose compounds of the following general **non-aromatic** piperazine-containing structure:



See column 8, lines 26-35. The **non-aromatic** piperazine-containing substitutent (i.e, the outlined portion) such as that cited in Example 23 corresponds to the R^6 position of the instant Formula III. Thus, for the compounds disclosed by Dorwald et al. to anticipate the instant claims of Formula III, the definition of R^6 must encompass the **non-aromatic** piperazine-containing structure illustrated above.

Even under the broadest reasonable construction in light of Applicants' specification, one of skill in the art would not construe R^6 to encompass the **non-aromatic** piperazine-containing structure. While R^6 encompasses the substitutent $-CH=CH-R^{44}$ where R^{44} can be $-COR^{46}$, the definition of R^{46} is hydrogen, alkyl, and aryl. The definition of the term aryl as set forth on page 6 of the specification is "a carbocyclic **aromatic** ring radical or to a fused **aromatic** ring system radicial" and can not be construed to include a piperazine ring because a piperazine ring is not

aromatic.

Thus, the rejection of claims 2, 5-7 and 14 under 35 U.S.C. §102(e) is without basis. Dorwald et al. fail to disclose the elements of claim 2. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. §103

Claim 15 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Dorwald et al. The rejection rests on the grounds set forth in the rejection under 35 U.S.C. §102(e) above. The Examiner additionally states that Dorwald et al. "teach that aryl, namely phenyl, can be also substituted with one or more of cation containing substitutents..." The Examiner then concludes that Dorwald et al. do not specifically mention the use of a cation form but that determination of a "cation" would have been apparent to those skilled in the art under 35 U.S.C. §103.

For the reasons sets forth above, the rejection of claim 15 under 35 U.S.C. §103(a) is also without basis. Further, while not necessary to overcome the rejection in light of the misapplication of Dorwald et al., Applicants also disagree with the Examiner's assertions regarding a cation form. Applicants respectfully request withdrawal of the rejection.

Fees

A response to the August 21, 2009 Office Action was originally due November 21, 2009. Applicants hereby petition for a 3-month extension of time and include herewith a petition under 37 C.F.R. § 1.136(a) and the appropriate fee. With a 3-month extension of time, a response is due February 21, 2010. However, since February 21, 2010 was a Sunday, a response filed the next business day, i.e. Monday, February 22, 2010 shall be considered timely.

The Commissioner is authorized to charge a three-month extension of time fee to Deposit Account No. 50-4674. Applicants do not believe further fees are due at this time; however, if any fee is deemed due, please consider this a petition therefore, with authority to charge the same deposit account.

CONCLUSION

Applicants believe the claims are in condition for allowance. If there are any questions regarding this Reply or the application in general, Applicants encourage a telephone call to the

undersigned in an effort to expedite the prosecution of the application.

Respectfully submitted,

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